DECLARATION

I, Yoshiaki TODAKA of c/o The Patent Corporate Body ARUGA PATENT OFFICE, 3-6, Nihonbashiningyocho 1-chome, Chuo-ku, Tokyo 103-0013 Japan do solemnly and sincerely declare that I well understand both Japanese and English languages and that I believe the attached English version is a true and complete translation of the Japanese Patent Application No. 2001-169261 filed on June 5, 2001 in the name of Kao Corporation.

March 3, 2005

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2001-169261

[Document Name] APPLICATION FOR PATENT

[Reference Number] P02411306

[Filed to] Commissioner, Patent Office

[International Classification] A61K 35/78

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[Designation of Fees]
[Number of Advance Payment Register] 011752
[Amount Paid] 21,000Yen

[List of Appended Documents]
[Document Name] Specification 1
[Document Name] Drawing 1
[Document Name] Abstract 1

[Request of Identification of Data] Requested

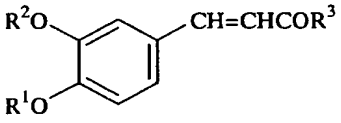
【Document Name】 SPECIFICATION

【Title of the Invention】 PREVENTIVE OR THERAPEUTIC AGENT FOR HYPERTENSION

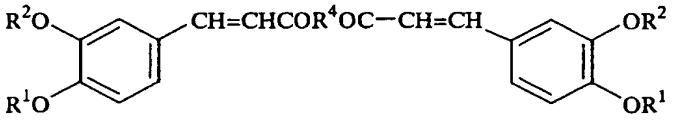
【Claims】

1. A preventive or therapeutic agent for hypertension, comprising a compound represented by the following formula (1) or (2):

【Chemical formula 1】



(1)



(2)

wherein, R^1 and R^2 are the same or different and each independently represents a hydrogen atom, an alkyl group, an alkenyl group, a cycloalkyl group, a cycloalkenyl group, an alkoxyalkyl group, an aryl group, an alkylaryl group, an aralkyl group or an acyl group, R^3 represents a hydroxyl group, an ester bond residue, or an amide bond residue, R^4 represents an ester bond residue or an amide bond residue, or a pharmaceutically acceptable salt thereof (except ferulic acid).

【Detailed Description of the Invention】

【0001】

【Field of the Invention】

The present invention relates to a preventive or therapeutic agent for hypertension.

【Description of the Related Art】

Cardiac diseases such as angina pectoris, myocardial infarction and heart failure, and cerebrovascular diseases such as cerebral infarction, cerebral hemorrhage and subarachnoid hemorrhage have a close relation to hypertension and they are,

respectively, the second and third leading causes of death among Japanese. According to National Livelihood Survey (fiscal 1998) of Health and Welfare Ministry, out of 1000 patients attending a hospital, 64 patients go there for treating hypertension and it is the first leading cause of disease in Japan. For the treatment of hypertension, employed is drug therapy using an antihypertensive such as diuretic, sympatholytic depressant, vasodilator or angiotensin converting enzyme inhibitor. Therapy with such a drug is applied mainly to patients with serious hypertension. General treatment for lifestyle modification including dietetic therapy, therapeutic exercise and cessation of drinking or smoking is, on the other hand, employed for patients at various stages of hypertension from mild hypertension to severe hypertension. Importance of the general treatment has therefore been recognized recently. Of the general treatments, improvement in eating habits is said to be important. There exists a number of foods which have traditionally been said to have an antihypertensive action. In addition, antihypertensive materials derived from foods have been searched extensively, and many active ingredients having an antihypertensive action have been separated or isolated.

【0003】

【Problems to be solved by the Invention】

Although many of the drugs employed to treat hypertension are satisfactory in their effectiveness, they are not completely free from side effects such as tachycardia and bradycardia and place a heavy burden on patients. Foods which are said to have an antihypertensive action, or active ingredients thereof do not always have satisfactory effectiveness and many of them need enough time to exhibit their antihypertensive effect fully. Recently, it has been found that ferulic acid exhibits a high hypertension ameliorating effect while having less side effects (Japanese Patent Application No. 2000-107957). Yet there has been a problem that the antihypertensive effect of ferulic acid cannot last over

a long period of time because of its high metabolic rate as measured in vivo.

An object of the present invention is therefore to provide a preventive or therapeutic agent for hypertension which has a long lasting antihypertensive effect so that the number of administration per day can be reduced, has a high degree of safety, does not impose a large stress on patients upon intake of it and has a higher antihypertensive action.

【0004】

【Means of Solving the Problems】

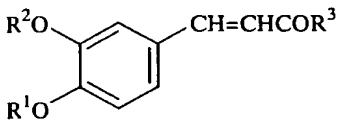
The present inventor has found that ferulic acid has an antihypertensive action, but owing to a high metabolic rate in vivo, its blood level reaches the maximum about 2 hours after administration and its metabolism and excretion are completed only after about 4 hours, while a specific compound having a ferulic acid skeleton has a long lasting antihypertensive effect because the compound after oral administration is metabolized into ferulic acid and this ferulic acid exists in the blood for a long time. The present inventor has also found that a compound having the specific ferulic acid skeleton is reduced in bitterness peculiar to ferulic acid and therefore has an improved taste, thereby allowing patients to take a large amount thereof.

【0005】

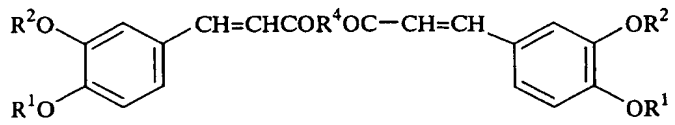
The present invention provides a preventive or therapeutic agent for hypertension comprising a compound represented by the following formula (1) or (2):

【0006】

【Chemical formula 2】



(1)



(2)

【0007】

wherein R^1 and R^2 are the same or different and each independently represents a hydrogen atom, an alkyl group, an alkenyl group, a cycloalkyl group, a cycloalkenyl group, an alkoxyalkyl group, an aryl group, an alkylaryl group, an aralkyl group or an acyl group, R^3 represents a hydroxyl group, an ester bond residue or an amide bond residue, R^4 represents an ester bond residue or an amide bond residue, or a pharmaceutically acceptable salt thereof (except ferulic acid).

【0008】

【Description of the Preferred Embodiment】

The compounds of the formula (1) or (2) to be used in the invention can be extracted from natural substances containing them, particularly plants, while they can be prepared industrially by chemical synthesis.

Preferred examples of the plants include coffee, apple, grape, onion, Japanese radish, lemon, *Cnidium officinale*, *Angelicae* radix, turpentine tree, *Coptis Rhizome*, turmeric, *Ferula assafoetida* L., sweet potato, leaves of sunflower, seeds of sunflower, jew's mallow sugarcane, corn, wheat, barley and rice, with rice being particularly preferred. The term "rice" as used herein means raw or dry seeds of rice (*Oryza sativa* LINNE).

【0009】

The compounds represented by the formula (1) or (2) include those prepared by chemical treatment of the extract or fraction, which has been obtained from a natural substance,

particularly, a plant; and those prepared by chemical modification of the natural substance. For example, a rice bran oil obtained from rice bran is separated using hydrous ethanol and hexane and then ethyl ferulate is available from the hydrous ethanol fraction.

【0010】

Ferulic acid, which is the skeleton of the compound represented by the formula (1) or (2), can be obtained by hydrolysis of a ferulate ester obtained by the foregoing process with hot sulfuric acid under pressure, followed by purification; or by culturing bacteria (*Pseudomonas*) in a broth containing a clove oil obtained by steam distillation of buds and leaves of *Syzygium aromaticum* MERRILL et PERRY or a broth containing eugenol available by purification of the clove oil, followed by separation of the resulting culture broth and purification. When ferulic acid is prepared by chemical synthesis, condensation reaction of vanillin with malonic acid can be employed (Journal of American Chemical Society, **74**, 5346(1952)). Incidentally, ferulic acid has stereoisomers. Any one of them is usable. A mixture of the isomers is also usable. Any ferulic acid obtained by the aforementioned methods is used as a starting material and can be converted into a derivative wherein R^1 and R^2 are the same or different and each independently represents a hydrogen atom, an alkyl group, an alkenyl group, a cycloalkyl group, a cycloalkenyl group, an alkoxyalkyl group, an aryl group, an alkylaryl group, an aralkyl group or an acyl group, R^3 represents a hydroxyl group, an ester bond residue or an amide bond residue, R^4 represents an ester bond residue or an amide bond residue.

【0011】

Examples of the alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxyalkyl, aryl, alkylaryl and aralkyl groups in the formulas (1) and (2) include groups derived from C_{1-40} alcohols. Examples of such alcohols include linear or branched alkyl or alkenyl alcohols, aryl alcohols, monoterpene alcohols, sesquiterpene alcohols, diterpene alcohols, triterpene alcohols, sterols,

and trimethyl sterols. Specific examples include methanol, ethanol, glycerol, oleyl alcohol, 2-ethylhexyl alcohol, allyl alcohol, cetyl alcohol, menthyl alcohol, phenol, benzyl alcohol, cholesterol, cycloartenol, 24-methylenecycloartenol, campesterol, β-sitosterol, cycloartanol, cycloprenol, α-sitosterol, stigmasterol, stigmastanol, α-sitostanol, β-sitostanol and campestanol. As R^1 and R^2, methyl and ethyl are preferred in terms of the metabolic time adopted as a barometer, from the viewpoint of durability of antihypotensive effect, with methyl being particularly preferred.

【0012】

Examples of the acyl group represented by R^1 or R^2 include acyl groups derived from C_{1-40} carboxylic acids. Examples of such carboxylic acids include linear or branched alkyl or alkenylcarboxylic acids, arylcarboxylic acids, monoterpenecarboxylic acids, sesquiterpenecarboxylic acids, diterpenecarboxylic acids, triterpenecarboxylic acids and sterolcarboxylic acids. Specific examples include formic acid, acetic acid, lactic acid, citric acid, gluconic acid, fumaric acid, α-ketoglutaric acid, succinic acid, glycolic acid, malic acid, tartaric acid, pyruvic acid, malonic acid, butyric acid, caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, valeric acid, enanthic acid, pelargonic acid, margaric acid, myristoleic acid, palmitoleic acid, petroselinic acid, oleic acid, vaccenic acid, linolic acid, linolenic acid, eleostearic acid, gatoleic acid, arachidonic acid, erucic acid, glucuronic acid and mevalonic acid.

【0013】

As the carboxylic acid residues of R^1 and R^2, formic acid residue and acetic acid are preferred from the viewpoint of stability of the compounds, with acetic acid being particularly preferred.

【0014】

Examples of the ether-bonded residues and the ester-bonded residues of R^1 and R^2 include those derived from

water-soluble amino acids. Specific examples of the amino acid residues usable for ether-bonding include serine, threonine and tyrosine. Specific examples of the amino acid residues usable for ester-bonding include glycin, alanine, valine, leucine, isoleucine, phenylalanine, proline, serine, threonine, cysteine, cystine, methionine, triptophan, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine and histidine. Of these, glycin and tyrosine are preferred in terms of the metabolic time adopted as a barometer, from the viewpoint of durability of antihypotensive effect, with glycin being particularly preferred.

【0015】

The group R^3 is, as well as a hydroxyl group, a residue ester-bonded or amide-bonded to the carboxyl group of a ferulic acid skeleton. The ester-bonded residues include residues derived from linear or branched, monohydric or polyhydric alcohols having 1 to 40 carbon atoms. Examples of the alcohols include alkyl or alkenyl alcohols, aryl alcohols, monoterpene alcohols, sesquiterpene alcohols, diterpene alcohols and triterpene alcohols. Specific examples include monohydric alcohols such as methanol, ethanol, propanol, butanol, pentanol, hexanol, heptanol, octanol, nonanol, decanol, undecanol, dodecanol, tridecanol, tetradecanol, pentadecanol, hexadecanol, heptadecanol, octadecanol, nonadecanol, eicosanol, heneicosanol, docosanol, tricosanol, tetracosanol, oleyl alcohol, 2-ethylhexyl alcohol, allyl alcohol, cetyl alcohol, menthyl alcohol, phenol, benzyl alcohol, and diacyl glycerol; and polyhydric alcohols such as glycerol, monoacylglycerol and phosphatidylglycerol.

【0016】

Examples of the ester-bonded residue include those derived from hydroxyl-containing carboxylic acids.

The hydroxyl-containing carboxylic acids include carboxylic acids containing one hydroxyl group such as citric acid, isocitric acid, malic acid, glycolic acid, cumaric acid, ferulic acid, isoferulic acid, vanillic acid, and homovanillic

acid; and carboxylic acid containing two or more hydroxyl groups such as gluconic acid, tartaric acid, quinic acid, Shikimic acid, caffeic acid, gallic acid, vanillylmandelic acid, glucuronic acid and mevalonic acid.

Of these hydroxyl-containing carboxylic acids, quinic acid, Shikimic acid, cinnamic acid, cumaric acid, citric acid, caffeic acid, ferulic acid, dimethoxycinnamic acid, gallic acid, and glucuronic acid are preferred in terms of the metabolic time adopted as a barometer, from the viewpoint of durability of an antihypertensive effect, with quinic acid being especially preferred.

【0017】

Residues derived from sugar alcohol or saccharide are mentioned.

Examples of the sugar alcohols include natural sugar alcohols, especially those contained in plants, sugar alcohols obtained by subjecting plants to chemical treatment upon extraction and/or fractionation, and sugar alcohols obtained by chemical modification of natural ones. Specific examples include alcohols obtained by the reduction of the carbonyl group of a monosaccharide, oligosaccharide or polysaccharide. Monosaccharide alcohols include erythritol which is a four-carbon sugar alcohol obtained by fermentation and decomposition of D-glucose with a yeast, xylitol which is a five-carbon sugar, sorbitol which is a six-carbon sugar, and mannitol. Specific examples of oligosaccharide include palatinit (hydrogenated palatinose), maltitol (hydrogenated maltose), lactitol and branched oligosaccharide alcohol. Polysaccharide alcohols include hydrogenated dextrin used as a glutinous starch syrup.

Of these sugar alcohols, erythritol, xylitol, sorbitol, and mannitol are preferred for an R^3 residue in terms of the metabolic time adopted as a barometer, from the viewpoint of durability of an antihypertensive effect, with erythritol being especially preferred.

Examples of saccharide include arabinose, galactose,

glucose, fructose, mannose, ribose, maltose, cellobiose, sucrose and lactose and polymers thereof. Of these, arabinose and galactose, and polymers thereof are especially preferred.

【0018】

Examples of the amide-bonded residues as R^3 include those derived from water soluble amino acids. Specific examples of such amino acids include glycine, alanine, valine, leucine, isoleucine, phenylalanine, proline, serine, threonine, cysteine, cystine, methionine, tryptophan, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine and histidine. Of these amino acids, glycine and tyrosine are preferred in terms of the metabolic time adopted as a barometer, from the viewpoint of durability of antihypertensive effect, with glycine being especially preferred.

【0019】

As the groups R_3, residues such as ethanol, docosanol, tetracosanol, quinic acid, citric acid, glucuronic acid, arabinose, gallic acid and glycine are preferred in the case where the metabolic time is taken as a barometer.

【0020】

The group R^4 represents any one of ester-bonded residues and amide-bonded residues, of which preferred are ester-bonded residues such as residues derived from polyhydric alcohols such as glycerol, monoacyl glycerol and phosphatidylglycerol; residues derived from carboxylic acid having at least 2 hydroxyl groups such as gluconic acid, tartaric acid, quinic acid, Shikimic acid, caffeic acid, gallic acid, vanillylmandelic acid, glucuronic acid, and mevalonic acid; and residues derived from sugar alcohols or saccharides. When the group R^4 is a residue derived from sugar alcohols or saccharides, the sugar alcohols or saccharides described above as R^3 are usable as R^4.

【0021】

As the group R^4, residues of arabinose, gallic acid, quinic acid and glucuronic acid are preferred in terms of the metabolic time adopted as a barometer.

【0022】

The compounds represented by the formula (1) or (2) are available by direct extraction from natural substances. In this case, they are prepared as a mixture of an ester compound, amide compound and ether compound. For instance, extraction is available from chlorogenic acid-containing plants, such as raw coffee beans, leaves of a nandina and unripe apple fruits. Alternatively, it is also possible to use an extraction obtained from the seeds of *Coffea arabica* LINNE with a warm aqueous solution of ascorbic acid or citric acid.

Specific examples of chlorogenic acids include 3-caffeoylquinic acid (neochlorogenic acid), 4-caffeoylquinic acid (cryptochlorogenic acid), 5-caffeoylquinic acid, 3,4-dicaffeoyl quinic acid, 3,5-dicaffeoil quinic acid, 4,5-dicaffeoyl quinic acid, 3-feruloylquinic acid, 4-feruloylquinic acid, 5-feruloylquinic acid, and 3-feruloyl-4-caffeoylquinic acid.

Examples of the extract from other plants include dimethyl caffeate ether, 2-O-caffeoyl-albutin, caffeoyl-calleryanin, 3-O-caffeoyl-shikimic acid, docosanol (C22) caffeate ester, eicosanol (C20) caffeate ester, heneicosanol (C21) caffeate ester, tricosanol (C23) caffeate ester, tetracosanol (C24) caffeate ester, pentacosanol (C25) caffeate ester, hexacosanol (C26) caffeate ester, docosanol ferulate ester, eicosanol ferulate ester, heneicosanol ferulate ester, tricosanol ferulate ester, tetracosanol ferulate ester, pentacosanol ferulate ester, hexacosanol ferulate ester, eicosyl ferulate ester, fukinolic acid, echinacoside, 1,3-dicaffeoylquinic acid, cichoric acid, coniferyl alcohol, curcumin, lignan and lignine.

Of these natural substances, 3-caffeoylquinic acid (neochlorogenic acid), 4-caffeoylquinic acid (cryptochlorogenic acid), 5-caffeoylquinic acid, 3,4-dicaffeoylquinic acid, 3,5-dicaffeoylquinic acid, 4,5-dicaffeoylquinic acid, 3-feruloylquinic acid, 4-feruloylquinic acid, 5-feruloylquinic acid,

3-feruloyl-4-caffeoylquinic acid, 1,3-dicaffeoylquinic acid, lignan, and curcumin are preferred in terms of the metabolic time adopted as a barometer, from the viewpoint of durability of an antihypertensive effect, with 5-caffeoylquinic acid being especially preferred.

【0023】

Of the compounds represented by the formula (1) or (2), preferred examples of the residues R^1 and R^2 include methyl, acetyl and glycin. Preferred examples of the residue R3 include ethanol, docosanol, tetracosanol, quinic acid, citric acid, arabinose, gallic acid, glycin and glucuronic acid. Preferred examples of R^4 include residues of arabinose, gallic acid, guinic acid and glucuronic acid. Specific examples include caffeoyl glucuronide, caffeoylglycine, feruloylglycine, feruloyl-arabinose, 3-feruloyl-4-caffeoyl arabinose, 3-caffeoylquinic acid, 4-caffeoylquinic acid and 5-caffeoylquinic acid.

【0024】

The compounds represented by the formula (1) or (2) have improved water solubility and enhanced physiological availability when they are in the form of a pharmaceutically acceptable salt. No particular limitation is imposed on the salt of ferulic acid insofar as it is pharmaceutically acceptable. Examples of a basic substance for the formation of such a salt include hydroxides of an alkali metal such as lithium hydroxide, sodium hydroxide and potassium hydroxide, hydroxides of an alkaline earth metal such as magnesium hydroxide and calcium hydroxide, inorganic bases such as ammonium hydroxide and basic amino acids such as arginine, lysine, histidine and ornithine, and organic bases such as monoethanolamine, diethanolamine and triethanolamine. Of them, hydroxides of an alkali metal or alkaline earth metal are particularly preferred.

The preventive or therapeutic agent for hypertension according to the present invention may be prepared by first preparing a salt of the above-described compound and adding the

salt into a composition made of other components, or by adding ferulic acid and a salt-forming component therewith to the composition separately, thereby forming the salt in the resulting mixture.

【0025】

The compounds represented by the formula (1) or (2) themselves may be used in combination.

The preventive or therapeutic agent for hypertension according to the present invention is preferably administered to an adult (weight: 60 kg) in an amount of about 0.01 to 50 g, preferably about 0.03 to 20 g, more preferably about 0.05 to 10 g a day in terms of ferulic acid. When a plant extract is employed, the amount in terms of dry weight can be administered.

【0026】

The preventive or therapeutic agent for hypertension according to the present invention can be prepared as an orally administrable or parenterally administrable composition by adding to its effective ingredient a pharmaceutically acceptable carrier. Of them, the orally administrable composition is preferred. Examples of the orally administrable composition include tablets, granules, fine subtilaes, pills, powders, capsules (including hard capsules and soft capsules), troches, chewables and liquids (medical drinks).

【0027】

The preventive or therapeutic agent for hypertension according to the present invention has a high degree of safety so that no problem occurs even if those who have a normal blood pressure usually take it as a food or beverage. The preventive or therapeutic agent for hypertension of the present invention can be taken as a beverage such as juice or coffee, a liquid food such as soup, an emulsion or pasty food such as milk or curry, a semi-solid food such as jelly and gummy, a solid food such as gum, tofu or supplement, a powdery food, or an oil- or fat-containing food such as margarine, mayonnaise or dressing.

The compound of the present invention is added to such a beverage or drink in an amount of 0.001 to 50 wt.%, preferably 0.01 to 25 wt.%, more preferably 0.1 to 10 wt.%. The content of ferulic acid is confirmed by high-performance liquid chromatography equipped with an electrochemical detector.

【0028】

Examples

Example 1: Identification of an antihypertensive component

1) Animals provided for test

Each of 15 week-old, spontaneously hypertensive male rats ("SHR") was anesthetized and its blood pressure was measured at the carotid artery by using a commercially available noninvasive sphygmomanometer for rats (manufactured by Softlon Co., Ltd.). Its electrocardiograph was recorded by an electrocardiogram. A sample was injected to the femoral vein through a catheter. After the rats were accustomed sufficiently to the sphygmomanometric operation, the evaluation test was started. The rats were all bred under conditions (in a breeding room in a rat region) at a room temperature of 25 ± 1°C, humidity of 55 ± 10% RH and illumination for 12 hours (from 7:00 am to 7:00 pm).

【0029】

(2) Administration method and amount

In the control plot, physiological saline was employed. In Test plot 1, Test plot 2 and Test plot 3, a solution of 5 μmol/kg caffeic acid in physiological saline, a solution of 5 μmol/kg quinic acid in physiological saline and a solution of 5 μmol/kg ferulic acid in physiological saline were used, respectively.

【0030】

(3) Test method

Through a catheter, the sample was intravenously administered and while administration, systolic blood pressures of the carotid artery were measured with the passage of time.

【0031】

As is apparent from FIG. 1, fluctuations in the blood pressure was not recognized when caffeic acid or quinic acid was intravenously administered, while lowering in the blood pressure was recognized when ferulic acid was administered. This result indicates that the effect of chlorogenic acids could be induced due to the conversion into ferulic acid by the metabolism in blood.

【0032】

Example 2: Measurement of an antihypertensive effect

1) Animals provided for test

After each of 15 week-old, spontaneously hypertensive male rats ("SHR") was accustomed to sphygmomanometric operation by preliminarily measuring its blood pressure for 7 successive days using a commercially available noninvasive sphygmomanometer for rats (manufactured by Softlon Co., Ltd.), the evaluation test was started. The rats were all bred under conditions (in a breeding room in a rat region) at a room temperature of 25 ± 1°C, humidity of 55 ± 10% RH and illumination for 12 hours (from 7:00 am to 7:00 pm).

【0033】

(2) Administration method and amount

In the test plot 1 (Comparative Example), a solution of ferulic acid (50 mg/kg as a dose) in physiological saline was employed. In Test plot 2, Test plot 3 and Test plot 4, a solution of chlorogenic acid (50 mg/kg as a dosage), chlorogenic acid (100 mg/kg as a dosage) and chlorogenic acid (200 mg/kg as a dosage) in physiological saline were used, respectively. In Test plot 5, oryzanol (50 mg/kg as a dosage) emulsified in physiological saline was employed. In each test plot, a physiological saline was used as a control.

【0034】

3) Test method

SHRs were fasted overnight and divided into groups, each consisting of 5 rats. Systolic blood pressures of the caudal artery were measured prior to administration, and several times during 30 minutes to 24 hours after administration.

【0035】

(4) Statistical treatment method

The test results thus obtained were expressed by the mean value (%) and standard deviation (SE) of the changing ratio (%) in systolic blood pressure.

【0036】

A lowering ratio of the systolic blood pressure measured during 30 minutes to 24 hours each after administration relative to the systolic blood pressure prior to administration is shown in Table 1.

【0037】

Table 1

	Time	0	0.5	1	2	3	4	6	9	12	24
Control	Mean	0	-0.5	-0.3	-2.1		0.2	-0.5			
	S.E	0	2.4	1.1	1.9		1.4	1.5			
Test plot 1	Mean	0	-9.5	-10.3	-6.8		-7.9	-3.2			
	S.E	0	1.5	1.1	1.4		1	1.7			
Control	Mean	0				-0.2		-1.3	-2.4	-2.2	-1.4
	S.E	0				1.5		1	1	1.1	1.8
Test plot 2	Mean	0				-4		-6.7	-7.3	-6.8	-2.9
	S.E	0				1.7		1.8	3.9	2.3	2.8
Test plot 3	Mean	0				-7.1		-10	-13.1	-11.8	-2.2
	S.E	0				1.2		1.7	2.6	1.9	2.4
Test plot 4	Mean	0				-7		-15.3	-15.7	-12.8	-2.90
	S.E	0				1.8		1.8	2.2	1.3	2.3
Control	Mean	0		-0.5	-2.2		-4.2				-
	S.E	0		0	0		0				
Test plot 5	Mean	0		-15.2	-12.8		-13.8				
	S.E	0		0	0		0				

【0038】

As is apparent from Table 1, rats in Test plots 2 to 5 each exhibited a long-lasting antihypertensive effect compared with

those in Test plot 1 (control).

【0039】

Example 3: Measurement of the blood ferulic acid concentration

(1) Animals provided for the test

Each of 15 week-old, spontaneously hypertensive male rats ("SHR") was preliminarily bred in a similar manner to Example 2.

(2) Administration method and amount

To the SHR, 200 mg/kg of chlorogenic acid was orally administered once.

(3) Test method

SHRs were fasted overnight and then divided into groups, each consisting of 5 rats. The blood levels of chlorogenic acid, caffeic acid and ferulic acid were measured prior to administration and several times during from 30 minutes to 24 hours, each after administration.

【0040】

The blood levels of chlorogenic acid, caffeic acid and ferulic acid measured prior to administration and several times during from 30 minutes to 24 hours, each after administration are shown in Table 2.

【0041】

Table 2

Time	0	3	6	9	12	24
Chlorogenic acid	0	0	0	0	0	0
Caffeic acid	0	0.07	0.179	0.166	0.05	0
Ferulic acid	0	0.074	0.154	0.174	0.145	0

【0042】

As is apparent from Table 2, not chlorogenic acid but caffeic acid and ferulic acid were detected in the blood. The time-dependent change has revealed the occurrence of in vivo conversion from caffeic acid into ferulic acid.

【0043】

Example 4: Measurement of the blood level of ferulic acid

(1) Test subject, administration method and administration amount

A beverage mixture containing an extract of raw coffee beans (chlorogenic acid group: 280 mg/day in terms of the amount of chlorogenic acid) was fed to 5 healthy subjects for successive 6 weeks. From the patients who did not take breakfast, the blood was collected 24 hours after final drinking. The blood was also collected under similar conditions from the group (placebo group: 0 mg/kg of chlorogenic acid administered, the group consisting of 3 subjects) free from the successive application of the above-described beverage mixture containing an extract from raw coffee beans.

(3) Test method

The blood levels of chlorogenic acid, caffeic acid and ferulic acid were measured using liquid chromatography.

【0044】

Table 3

(μg/mL plasma)

	Placebo group	Chlorogenic acid group
Caffeic acid	0.009	0.0954
Ferulic acid	0	0.1044
Chlorogenic acid	0	0

【0045】

The results are as shown in Table 3. In the blood, not chlorogenic acid but caffeic acid and ferulic acid were observed. In vivo conversion of caffeic acid to ferulic acid was observed with time.

【0046】

Example 5: Soft capsules

Gelatin	70.0 (wt.%)
Glycerin	22.9
Methyl paraoxybenzoate	0.15
Propyl paraoxybenzoate	0.51
Water	6.44

Soft capsules (oval-type, weight: 150 mg) composed of the above-described composition were filled with 400 mg of soybean oil, 50 mg of dicaffeoyl tartaric acid and 50 mg of eicosanol

caffeate in a manner known per se in the art. These capsules exhibited a good antihypertensive action when orally administered.

【0047】

Example 6

The exemplified use as a beverage will next be described.

Skim milk	3.5 (wt.%)
Enzyme-hydrolyzed milk casein	3.5
Fructose	9.0
Eicosylferulate ester	0.1
3-Feruloyl-4-caffeoylarabinose	10.0
Citric acid	0.1
Ascorbic acid	0.1
Flavor	0.1
Water	73.6

It has been found that the beverage made of the above-described composition had high storage stability and had good taste.

【0048】

Example 7

An application example to wheat flour products will next be described.

Rapeseed oil	15 (g)
Corn starch	15
Wheat flour	42.6
Butter	5
Fructose	14
Caffeoylglycine	2
Ferulyl-citric acid	0.4
Table salt	0.5
Sodium bicarbonate	0.5
Water	5

Cookies made of the above-described composition were baked.

【0049】

【Effect of the Invention】

When the preventive or therapeutic agent for hypertension according to the present invention is administered, ferulic acid exists in the blood for a long period of time, thereby continuously suppressing a blood pressure rise. Moreover, this agent has reduced in bitterness peculiar to ferulic acid, which enables patients to take it continuously.

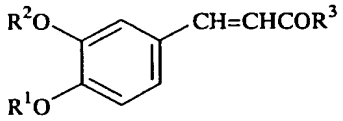
【Brief Description of the Drawing】

FIG. 1 illustrates identification of an antihypertensive component.

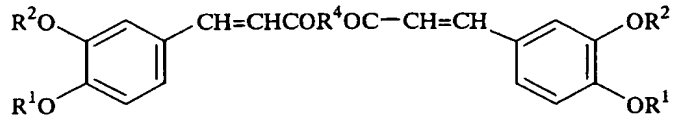
ABSTRACT

Provided is a preventive or therapeutic agent for hypertension comprising a compound represented by the following formula (1) or (2):

【Chemical formula 1】



(1)



(2)

wherein, R^1 and R^2 are the same or different and each independently represents hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxyalkyl, aryl, alkylaryl, aralkyl or acyl, R^3 represents hydroxyl, ester bond residue or amide bond residue, R^4 represents ester bond residue or an amide bond residue, or a pharmaceutically acceptable salt thereof (except ferulic acid).

【Effect】 When the preventive or remedy for hypertension according to the present invention is administered, ferulic acid exists in the blood for a long period of time, thereby continuously suppressing a blood pressure rise. Moreover, the hypertension preventive or remedy according to the present invention has reduced in bitterness peculiar to ferulic acid, which enables patients to take it continuously.

【Selected Drawing】 None

【Document Name】 DRAWING

【Fig. 1】